

Response to I. Batinic-Haberle et al.

Citation for published version (APA):

Schmidt, H. H. H. W., Stocker, R., Paulsen, G., Ghezzi, P., Riley, D., Daiber, A., & Cuadrado, A. (2016). Response to I. Batinic-Haberle et al. *Antioxidants & Redox Signaling*, 24(9), 525-526. <https://doi.org/10.1089/ars.2016.29029.hhs>

Document status and date:

Published: 20/03/2016

DOI:

[10.1089/ars.2016.29029.hhs](https://doi.org/10.1089/ars.2016.29029.hhs)

Document Version:

Publisher's PDF, also known as Version of record

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Response to I. Batinic-Haberle *et al.*

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To the Editor:

THE LETTER BY Batinic-Haberle *et al.* (3) in response to our review (7) is symptomatic for our exciting field of redox biology and medicine, although we disagree with its aggressive and in part nonscientific style. Their focus appears to be on redox biology, whereas the focus of our review was on redox medicine, in particular those drugs and applications already in clinical practice or in advanced clinical development rather than of “potential” or “future” clinical relevance. It was beyond the scope of our review to address the wide field of redox biology or experimental antioxidant reagents. Batinic-Haberle *et al.* (3) provide a good overview of redox-active compounds that, based on preclinical data, might hold some promise for clinical developments [see table 1 in (3)]. To our knowledge, however, just a few of these compounds had entered a phase I trial at the time of writing our review, and none of them had progressed to phase II. One exception is mitoQ for which several phase II trials have been carried out in Parkinson’s disease, aging, nonalcoholic fatty liver disease, and hepatitis C, although none of these trials has been conclusive. In addition, the phase III study 2CARE for Huntington’s disease has been halted prematurely as a result of lack of efficacy of coenzyme Q₁₀ (<http://huntingtonstudygroup.org/tag/2care/>).

Batinic-Haberle *et al.* (3) specifically criticize that superoxide dismutase (SOD) mimetics were not mentioned, when in fact our review did mention some of these compounds, although maybe not the ones favored by these authors. AEOL 10150 may be an interesting antioxidant, but it has been at an early clinical stage of development for many years. Moreover, a phase I trial with amyotrophic lateral sclerosis (also known as Lou Gehrig’s disease and Charcot disease) patients

in 2005 did apparently not progress, and in January 2015, the FDA put a clinical hold on AEOL 10150 (www.marketwired.com/press-release/aeolus-announces-response-fda-clinical-hold-plan-clinical-development-aeol-10150-otcqb-aols-1981367.htm). MnSOD mimetics were also discussed in cancer prevention and chronic obstructive pulmonary disease, but clinical trials are lacking (5). Other related compounds for which the authors of the letter appear to have a special interest, such as BMX-010 and BMX-001, are, to our knowledge, still in phase I, and we note that some of the authors of the letter hold patents for some of these compounds (4) and are supported by the company developing them (*i.e.*, Biomimetix Pharmaceutical, Inc).

Conversely, the SOD mimetic mentioned in our review, GC4419, as being, at that time, in phase IIa was meanwhile shown to protect patients from side effects of radiotherapy (www.evaluategroup.com/Universal/View.aspx?type=Story&id=616252). Based on these clinical trial results, the US FDA has granted “Fast-Track” status to this agent in December 2015 and the compound is now in a phase IIb/IIIa human clinical trial in the United States at several major cancer treatment centers and shall be completed in approximately 1–2 years. To the best of our knowledge, this development stage is the most advanced in the field and it is thus appropriate to have focused on this compound.

We note that the letter of Batinic-Haberle *et al.* (3) also contains a textbook-style lecture on SOD catalysis being a one-electron process. We agree, of course, that true SOD catalysis is a one-electron process. However, the same is not the case for the Mn(porphyrin) complexes described by Batinic-Haberle *et al.* (3), as these also carry out multiple electron processes. For example, the same group reported Mn(porphyrin) complexes to also be good “catalase”

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mimics (2) and others described them as efficient peroxynitrite decomposition catalysts (8). Thus, they are not only selective for superoxide removal but also react with the product of the dismutation, hydrogen peroxide, and the secondary oxidant, peroxynitrite. This may or may not be clinically useful or relevant, but mechanism is something that must be noted when discussing pharmacology of a pharmaceutical agent.

Furthermore, it is irritating that the authors attempt to discount other compounds that are currently in human clinical trials [e.g., Mn(II)pentaazamacrocyclic ligand complexes] by claiming that they are acid unstable. This is misleading given that some of the authors of this letter have reported previously on the high kinetic and thermodynamic stability of members of this class of compounds (e.g., M40403) (6). In fact, compounds of this class, including GC4419, are largely unmetabolized (>90% unchanged) and excreted almost entirely intact (1).

In summary, given the focus of our review on the advanced clinical stage of antioxidant drugs, we consider it free of obvious bias, including conflict of interest. By comparison, it would have been appropriate for the authors of the letter, in the version provided to us, to state any potential conflict of interest that may have contributed to their choice of compound(s).

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Date of first submission to ARS Central, January 29, 2016;
date of acceptance, February 6, 2016.

Abbreviation Used

SOD = superoxide dismutase